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Theresa DiJoseph

Philadelphia College of Osteopathic Medicine, theresadij@pcom.edu

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DiJoseph, Theresa, "Does Nicotine Replacement Therapy Reduce the Withdrawal Symptom of Craving, or Urge to Smoke, in Dependent Adult Smokers During Smoking Cessation?" (2013). *PCOM Physician Assistant Studies Student Scholarship*. Paper 148.

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Does nicotine replacement therapy reduce the withdrawal symptom of craving, or urge to smoke, in dependent adult smokers during smoking cessation?

Theresa DiJoseph, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2012

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not nicotine replacement therapy reduces the withdrawal symptom of craving, or urge to smoke, in dependent adult smokers during smoking cessation.

STUDY DESIGN: Systematic review of three English language and peer-reviewed randomized-controlled trials published in 2009, 2010, and 2011.

DATA SOURCES: One single-blinded randomized-controlled crossover trial, one double-blinded, placebo controlled, randomized-controlled crossover trial, and one single-blinded, placebo controlled, randomized-controlled crossover trial

OUTCOMES MEASURED: Withdrawal symptoms of craving, irritability, difficulty concentrating, and restlessness were measured on a 100mm visual analog scale (VAS). Adverse effects (AEs) of mouth and throat irritation, aching jaw, feeling sick, vomiting, flatulence/belching, stomachache, heartburn, diarrhea, hiccups, feeling high, feeling dizzy, headache, palpitations, sweatiness, and cold hands/feet were measured based upon their frequency and strength. One study measured slightly different withdrawal symptoms (depressed mood, irritability, restlessness, hunger, and poor concentration) on a Moods and Physical Symptoms Scale (MPSS) and time spent with urges and strength of urges on a six-point Likert Scale. This study also measured the adverse effects of feeling unwell, nausea, throat irritation, and dizziness on a 10-point scale. Temporary smoking cessation was measured in all three studies.

RESULTS: Thornley et al found that the active pouch significantly decreased craving in comparison to placebo. The gum decreased craving; however, the findings were not considered to be statistically significant. In McRobbie et al, all three types of NRT proved to significantly decrease craving in comparison to placebo. Similarly, Shahab et al found that both innovative and older types of NRT decreased craving. The Nicotine Cannon was more tolerable than older types of NRT. Overall, the NRT products caused more adverse reactions than placebo, but also led to more cases of temporary smoking cessation.

CONCLUSION: The results of all three studies show that nicotine replacement therapy decreases the withdrawal symptom of craving, allowing smokers to be more successful in their attempts to quit in the short term. No one NRT product is significantly better than another in decreasing craving.

KEY WORDS: nicotine replacement therapy, withdrawal, smoking cessation, craving

INTRODUCTION

Nicotine dependence is due to alkaloid nicotine, which is a chemical in cigarettes that alters the dopaminergic pathway in the midbrain and trains the brain to require nicotine to feel pleasure. Alkaloid nicotine binds to the naturally occurring nicotinic receptors in the human brain and spinal cord, sending a message of reward, or pleasure, throughout the body.¹ With repeated stimulation of these receptors, a person builds tolerance and requires higher levels of nicotine to feel the same positive effects. This unending cycle ultimately leads to the body's dependence on and addiction to nicotine. This paper evaluates three randomized-controlled trials that compare the efficacy of various types of nicotine replacement therapy (NRT) with placebo in preventing the withdrawal symptom of craving in adult smokers during smoking cessation.

Although the alkaloid nicotine is responsible for the addiction to cigarettes, it is actually the other toxins (benzene, carbon monoxide, acetic acid, formaldehyde, and heavy metals) that are responsible for the negative health effects of smoking. Cigarette smoking directly contributes to patients' health and frequently complicates chronic medical conditions and their treatments. Individuals who smoke are more likely to suffer from chronic pulmonary and cardiovascular diseases and various carcinomas, particularly of the lung, kidney, bladder, and cervix.² Women who smoke during pregnancy have a higher rate of spontaneous abortion and are at risk of giving birth to babies who are small for gestational age.³ Currently, the prevalence of cigarette smoking in the United States is 19.3%, with people between the ages of 18 and 64 being more likely to smoke than those over age 65.⁴ Because cigarette smoking is directly responsible for so many health problems, it is important for physician assistants to be knowledgeable of both the health

consequences of smoking and the smoking cessation options that are available for their patients.

Although the cost per day varies depending on personal habit, the average cost of a pack of cigarettes in the US is \$5.51.⁵ It is important to realize, however, that some smokers may have a multi-pack per day habit and could potentially be spending well over \$10 a day on a product that is only harming them. In fact, cigarette smoking leads to over \$100 billion in health care expenses, \$67 billion in productivity losses at work, and over \$100 billion in premature deaths annually.⁵ Whereas a tobacco addiction can be lifelong, treatment with NRT is only a temporary expense that will result in better health outcomes in the future. The average daily cost of NRT varies depending on the type of product one uses: nasal spray \$3.41, patches \$3.91, lozenges \$4.98, gum \$5.81, and inhaler \$6.07.⁶

Approximately 70% of current smokers in the US are interested in smoking cessation; however, they lack the knowledge of where to look for help and the emotional support that proves to be crucial in the process of smoking cessation.¹ Various methods of smoking cessation exist, such as behavioral modification, group counseling, Bupropion, Chantix, and NRT. Smoking cessation is an individualized process and may require more than one attempt before finding the appropriate method that leads to a successful outcome.

The withdrawal symptom of craving directly affects a smoker's ability to quit smoking by making it more difficult to resist cigarettes for long periods of time. By using NRT, smokers are able to deliver limited amounts of nicotine to their brains in order to decrease their craving and retrain their bodies to function without requiring nicotine.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not nicotine replacement therapy reduces the withdrawal symptom of craving, or urge to smoke, in dependent adult smokers during smoking cessation.

METHODS

Criteria used for the selection of the research articles for this review was based on population age (≥ 18 years old) and dependency on cigarette smoking. It was important for studies to include comparisons of various nicotine replacement products (4mg Zonnic® oral nicotine pouch, 4mg Nicorette® chewing gum, Zonnic® 1mg/spray mouth spray, Zonnic® 2.5mg nicotine lozenge) to the usage of placebo.^{7,8} One of the articles compared an innovative nicotine replacement therapy (the Nicotine Cannon) to older NRT products (nicotine inhaler, 4mg nicotine lozenge, and 4mg nicotine mini-lozenge).⁹ All articles assessed patient-oriented evidence that matters (POEMs), which included withdrawal symptoms, adverse effects of NRT usage, and temporary smoking cessation.

The author used the PubMed and Medline databases to search for peer-reviewed randomized-controlled trials that were published in the English language within the last five years. Important key words that were used included “nicotine replacement therapy,” “withdrawal,” “smoking cessation,” and “craving”. The articles were selected based upon their evaluation of POEMs and a participant pool of people ≥ 18 years old. Exclusion criteria comprised of patients less than 18 years of age, those not dependent on cigarette smoking, and articles that addressed disease-oriented evidence (DOE). The statistics reported in the studies included 95% confidence intervals (CI), p-values, change in mean from the baseline, independent t test, and χ^2 . The author calculated the numbers needed to treat (NNT) and numbers needed to harm (NNH) using the dichotomous data

on adverse effects and temporary smoking cessation in order to support the efficacy of NRT use in comparison to placebo in preventing the withdrawal symptom of craving.

Table 1. Demographics & Characteristics of Included Studies

Study	Type	# people	Mean Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Shahab ⁹ (2011)	RCT – single-blind, crossover	48	31	Over 18, regular smokers x at least a year, ≥ 5 cigarettes/d, in good health; not pregnant; not current users of NRT products	N/A	N/A	Nicotine Cannon; Nicotine lozenge (4mg); Mini-lozenge (4mg); Nicotine inhaler
McRobbie ⁷ (2010)	RCT - double-blind, crossover, placebo controlled	47	49	18 to 70 years old, smoked 15+ cigarettes/d for at least the last year, smoked first cigarette within 30 minutes of waking, in good health, able to read and write English and give written consent	Recent (previous 6 mo) MI, angina, DM, other serious medical condition, previous severe allergic reaction, current chemical dependence other than nicotine, current psychiatric d/o or current use of psychotropic drugs, chronic oral d/o that would prevent the use of oral NRT products, current use of nicotine products other than cigarettes, pregnancy or breast feeding, weight <45 kg or >120 kg, blood pressure BP >180/>100 or unwillingness to abstain from smoking prior to or during the study day	3	Zonnic 1 mg/dose mouth spray (two sprays between the cheek and gums q1h; more frequently if needed); Zonnic 2.5mg lozenges; Nicorette 4mg chewing gum (one piece each hour; more frequently if needed)
Thornley ⁸ (2009)	RCT – single-blind, crossover, placebo controlled	30	50	Same as McRobbie (2010)	Same as McRobbie (2010)	3	Zonnic 4mg oral nicotine pouch; Nicotine chewing gum (4 mg); one pouch/piece of gum per hour

OUTCOMES MEASURED

Outcomes measured across all three studies included withdrawal symptoms, adverse effects of NRT usage, and temporary abstinence from smoking throughout the duration of the study days. McRobbie et al and Thornley et al measured the following withdrawal symptoms: craving, irritability, difficulty concentrating, and restlessness. These were measured on a 100mm visual analog scale (VAS; 0= not at all; 100= extremely) every five minutes for a total of 60 minutes after the participant used the NRT product.^{7,8} These researchers also measured the adverse effects (AEs) of mouth and throat irritation, aching jaw, feeling sick, vomiting, flatulence/belching, stomachache, heartburn, diarrhea, hiccups, feeling high, feeling dizzy, headache, palpitations, sweatiness, and cold hands/feet based upon their frequency (never, often, or sometimes) and their strength (weak, moderate, and strong).^{7,8} The measurement for AEs as well as the measurement for temporary smoking cessation were made at the completion of each study day.

Shahab et al measured the withdrawal symptoms of depressed mood, irritability, restlessness, hunger, and poor concentration on a Moods and Physical Symptoms Scale (MPSS). This study also measured time spent with urges and strength of urges to smoke on a six-point Likert scale. Adverse effects, measured on a 10-point scale (0= none; 10= extreme), included feeling unwell, nausea, throat irritation, and dizziness. All of these measurements were taken via questionnaire before (0 minutes), during (3, 6, 10 minutes) and after NRT usage (13, 16, 20 minutes).⁹ Temporary smoking cessation was also measured at both one and ten hours after NRT usage.

The author focused on the withdrawal symptom of craving; however, the dichotomous data on adverse effects and temporary smoking cessation supported the research question.

RESULTS

Because the research question focuses on the prevention of craving, only the data regarding that withdrawal symptom will be presented in the following section. The data pertaining to two common adverse effects (mouth/throat irritation and feeling sick) as well as that of temporary smoking cessation provided support for the research question, so that data will be explained here too.

Two of the randomized-controlled trials compared various types of NRT to placebo and one of the randomized-controlled trials compared a new type of NRT to older types of NRT. The Thornley et al trial consisted of three study days, each separated by three days when the participants were instructed to smoke normally. The McRobbie et al trial consisted of four study days, each separated by three days when the participants were instructed to smoke normally. Finally, the Shahab et al trial consisted of four study days, each separated by seven days when the participants were instructed to smoke normally.

In the study by Thornley et al, 27 out of the 30 original participants completed the three study days. It was found that the active nicotine pouch was significantly superior in decreasing the participants' craving than the placebo pouch ($p= 0.002$); furthermore, there was a mean change in craving from baseline of -23.1 for the active pouch and only a mean change of -8.7 for the placebo pouch, making the mean difference -14.4 (Table 2).⁸ The gum did not significantly decrease craving in comparison to placebo ($p= 0.22$). Table 3 displays the data for treatment effect, showing that in comparison to the placebo

(41%), both the gum (52%) and the active pouch (75%) allowed more participants to remain abstinent throughout the study days.⁸ The relative benefit increase (RBI) was calculated to be 26.8% for the gum and 82.9% for the pouch; the absolute benefit increase (ABI) was 11% for the gum and 34% for the pouch. Finally, the numbers needed to treat (NNT) was nine for the gum and three for the pouch (Table 3). This means that nine people have to use the gum and three people have to use the active pouch in order for one person to temporarily abstain from tobacco use.

Table 4 displays the data describing two common adverse effects of both types of NRT versus placebo. The gum (33%) and the active pouch (13%) caused more people to feel sick than placebo (7%); similarly, the gum (47%) and the active pouch (50%) caused more people to experience mouth irritation than placebo (37%).⁸ The numbers needed to harm (NNH) were calculated for the gum and active pouch for both of the adverse effects. The NNH for feeling sick was four for the gum and 17 for the active pouch. This means that for every four people that use the gum and for every 17 people that use the active pouch, one person will feel sick. The NNH for mouth irritation was 10 for the gum and eight for the active pouch (Table 4).

Table 2. Mean change in craving from baseline to 60 minutes after taking medication⁸

Treatment	Mean	Mean difference with placebo	p-value
Active pouch	-23.1	-14.4 (-24.1 to -4.8)	0.002
Gum	-15.4	-6.7 (-16.4 to 2.9)	0.22
Placebo	-8.7	-----	-----

Table 3. Temporary smoking cessation until 5:30pm on study days⁸

CER	EER	RBI	ABI	NNT
41%	Gum: 52%	Gum: 26.8%	Gum: 11%	Gum: 9
	Active pouch: 75%	Active pouch: 82.9%	Active pouch: 34%	Active pouch: 3

Table 4. Adverse effects of the gum and active pouch vs. placebo⁸

Adverse event	CER	EER	RRI	ARI	NNH
Feeling sick	7%	Gum: 33% Active pouch: 13%	Gum: 371.4% Active pouch: 85.7%	Gum: 26% Active pouch: 6%	Gum: 4 Active pouch: 17
Mouth irritation	37%	Gum: 47% Active pouch: 50%	Gum: 27% Active pouch: 35.1%	Gum: 10% Active pouch: 13%	Gum: 10 Active pouch: 8

In the study by McRobbie et al, 44 out of the 47 participants completed all four study days. Table 5 shows that all three NRT products significantly reduced the withdrawal symptom of craving more than placebo. There was a mean change in craving from baseline of -24.7 for the lozenge, -25.8 for the gum, and -28.6 for the mouth spray in comparison to -8.9 for placebo, making the mean differences -15.8, -16.9, and -19.7 respectively (Table 5).⁷ Table 6 displays the data for treatment effect, showing that in comparison to the placebo (19%), the lozenge (45%), gum (55%) and the mouth spray (53%) allowed more participants to remain tobacco free throughout the study days.⁷ The RBI was calculated to be 137% for the lozenge, 190% for the gum, and 179% for the mouth spray; the ABI was 26% for the lozenge, 36% for the gum, and 34% for the mouth spray. Finally, the NNT was four for the lozenge, three for the gum, and three for the mouth spray (Table 6).

Table 7 displays the data describing two common adverse effects of the NRTs versus placebo. The lozenge (38%), gum (34%), and mouth spray (36%) caused more people to feel sick than placebo (4%); similarly, the lozenge (25%), gum (30%), and mouth spray (45%) cause more people to experience mouth irritation than placebo (4%).⁷ The NNH was calculated for the lozenge, gum, and mouth spray for both of the adverse effects. The NNH for feeling sick was three for all types of NRT (Table 7). The NNH

for mouth irritation was five for the lozenge, four for the gum, and two for the mouth spray (Table 7).

Table 5. Mean change in craving from baseline to 60 minutes after taking medication⁷

Treatment	Mean change	Mean difference with placebo (95%	p-value
Lozenge	-24.7	-15.8 (-23.7 to -7.9)	<0.0001
Gum	-25.8	-16.9 (-24.8 to -9.0)	<0.0001
Mouth spray	-28.6	-19.7 (-27.6 to -11.7)	<0.0001
Placebo	-8.9	-----	-----

Table 6. Temporary smoking cessation until 5:30pm on study days⁷

CER	EER	RBI	ABI	NNT
19%	Lozenges: 45%	Lozenges: 137%	Lozenge: 26%	Lozenge: 4
	Gum: 55%	Gum: 190%	Gum: 36%	Gum: 3
	Mouth spray:	Mouth spray: 179%	Mouth spray:	Mouth spray: 3

Table 7. Adverse effects of the lozenge, gum, and mouth spray vs. placebo⁷

Adverse	CER	EER	RRI	ARI	NNH
Feeling sick	4%	Lozenge: 38% Gum: 34% Mouth spray: 36%	Lozenge: 85% Gum: 80% Mouth spray: 75%	Lozenge: 34% Gum: 30% Mouth spray: 32%	Lozenge: 3 Gum: 3 Mouth spray: 3
Mouth irritation	4%	Lozenge: 25% Gum: 30% Mouth spray: 45%	Lozenge: 525% Gum: 650% Mouth spray: 1025%	Lozenge: 21% Gum: 26% Mouth spray: 41%	Lozenge: 5 Gum: 4 Mouth spray: 2

In the study by Shahab et al, 48 people participated in comparing the new Nicotine Cannon (NC) to pre-existing forms of NRT (lozenge, mini-lozenge, gum, and inhaler). The researchers of this study did not provide the author with dichotomous data; therefore, NNT and NNH could not be calculated. Shahab et al found that there were statistically significant reductions in both time spent with urges to smoke and strength of those urges from before NRT use to after NRT use across all types of NRT that were tested in this trial ($p < 0.0001$) (Table 8).⁹ Compared to the lozenge, mini-lozenge, and

nicotine inhaler, NC usage resulted in less reported adverse side effects, making it more attractive to those who are interested in smoking cessation.

Table 8. Reduction in withdrawal symptoms across all NRT products from before to after use⁹

Withdrawal Symptom	F-score	p-value
Time spent with urges	(1, 236) = 27.5	<0.0001
Strength of urges	(1, 213) = 40.9	<0.0001

DISCUSSION

In compiling the data across all three of the articles that were analyzed in this systematic review, the conclusion can be drawn that nicotine replacement therapy is more effective than placebo in preventing the withdrawal symptom of craving in smokers who are attempting to quit in the short term. However, with the small sample sizes and short study times, it is impossible to make such a generalized statement about the long term usage of NRT and smoking cessation.

Nicotine replacement therapy is widely available in the United States. The transdermal patch, lozenges, and gum are all available over the counter and do not require a prescription.¹⁰ However, it is important to inform your doctor that you are attempting to quit smoking and using an over-the-counter NRT product. The high amounts of nicotine in cigarettes change the body's metabolism; therefore, removing tobacco products from one's body may change the management of other chronic health problems. The mouth spray, nasal spray, and nicotine inhaler all require a prescription from a doctor, physician assistant, or other licensed medical provider.¹⁰

One of the major roadblocks to NRT usage is insurance coverage. Although it is improving, most private and state based insurances do not cover the entire cost of NRT. The American Lung Association has been making efforts to demonstrate how important it is for insurance companies to offer coverage for smoking cessation products. Currently,

only six states require Medicaid to cover smoking cessation products and only nine states require private insurances to cover smoking cessation products.¹¹ Last year, the federal government started providing coverage for smoking cessation products and counseling sessions for all of its employees.¹¹ With additional support from insurance companies, smokers will have more of an incentive to quit their habit and prevent many of the health complications that result from long term tobacco use.

All three of the studies included in this review had similar limitations and flaws in the performance of the research. The sample size of less than 50 participants for each study did not allow for adequate heterogeneity in order to be able to make a general statement about the efficacy of NRT among all types of dependent smokers. All three studies allowed the participants to smoke on the days in between the short 9-hour study days. In reality, smokers are not supposed to alternate using NRT with smoking cigarettes. Therefore, these studies did not adequately assess the correct usage of the products. Long term usage of these products could lead to the development of more adverse reactions that may affect people's compliance with the therapy.

CONCLUSION

According to the three studies in this review, nicotine replacement therapy is a safe and effective treatment in preventing the withdrawal symptom of craving in dependent smokers who are attempting to quit. However, the various limitations of the three included studies inhibit the author from generalizing the effectiveness of NRT to the entire population of dependent smokers. In future studies, it will be important to increase the sample size and the length of time that the participants use the NRT products. It is necessary to eliminate the series of non-study days in between study days in order to evaluate the correct usage of NRT. It would be interesting to divide the

participants according to the length of time that they have been smoking and frequency of their habit to see if NRT works equally as well for those with a longer and heavier habit history than others. Another possibility for further research would be to start a longitudinal study that assesses smoker's health before attempting to quit, follows them through the quitting process, and then checks in with them at certain intervals to see how successful they were in the long term.

Smoking cessation is a challenging and personal process; with continued research and support from insurance companies, dependent smokers will be able to successfully quit their habits and live healthier and longer lives.

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